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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,571	07/13/2007	**Glenn D. Prestwich**	67934-8006.US00	6987

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King & Spalding LLP
P.O. Box 889
Belmont, CA 94002-0889

EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
10/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,571	PRESTWICH ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,24,25,51-53,199,200,224-230,234-237,239,240 and 242-244* is/are pending in the application.

4a) Of the above claim(s) *199* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,24,25,51-53,200,227,228,236,239,240 and 242-244* is/are rejected.

7)☒ Claim(s) *224-226,229,230,234,235 and 237* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *19 March 2009 and 10 September 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed on 27 September 2010 in which claims 11-23, 26-50, 54-198, 201-223, 231-233, 238, 241, 245 and 246 were cancelled, and claims 1, 2, 4-10, 24, 25, 51-53, 199, 200, 224-230, 234-237, 239, 240 and 242-244 were amended, is acknowledged.

Claims 1-10, 24, 25, 51-53, 199, 200, 224-230, 234-237, 239, 240 and 242-244 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/US04/40726 filed on 6 December 2004 and claims priority to U.S. provisional application no. 60/526,797, filed on 4 December 2003.

Election/Restrictions

Applicants' election without traverse of Group I, claims 1-10, 24, 25, 49-55, 199, 200 and 224-246, now pending claims 1-10, 24, 25, 51-53, 199, 200, 224-230, 234-237, 239, 240 and 242-244, drawn to a modified glycosaminoglycan in which at least one hydroxyl group of the structure is modified such that the oxygen atom is covalently bound to a hydrazide-reactive group or an aminooxy-reactive group, in the reply filed on 27 September 2010 is acknowledged.

Furthermore, in response to a requirement for the election of a single disclosed species, Applicants elect (A) the reactive group as recited in claim 227, structure (III),

which has been incorporated by amendment into the limitations of claim 1, for a reactive group, and (B) living cells for additional components in the pharmaceutical compositions. With respect to the reactive group, it is noted that Applicants further elected a particular reactive group, and noted that the election was made if it was deemed necessary. However, in view of Applicants' amendment to the claims to encompass the elected reactive group into independent claim 1, it is not necessary for Applicants to further elect a particular reactive group other than that as recited in claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Claim 199 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 27 September 2010.

Claims 1-10, 24, 25, 51-53, 200, 224-230, 234-237, 239, 240 and 242-244 will be examined on its merits herein.

Information Disclosure Statement

The information disclosure statements (IDS) dated 19 March 2009 and 10 September 2009 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 236 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "DTPH" in claim 236 render the claim herein indefinite. Acronyms or abbreviations can be interpreted differently depending on the context and the art. For example, "EPA" can stand for "eicosapentaenoic acid" or it can be an abbreviation for the "Environmental Protection Agency". Thus, it is unclear whether "DTPH" refers to dithiobis(propanoic dihydrazide, or whether it is an acronym or abbreviation for something else. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim, rather than use acronyms or abbreviations. If Applicants intend to use acronyms or abbreviations in the claims, it is respectfully suggested that the acronym or abbreviation first be spelled out along with the acronym where it is first used in a claim before use of the acronym or abbreviation in subsequent claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 24, 25, 51-53, 200, 227, 228, 239, 240 and 242-244 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' amendment with respect to the amended claims herein has been fully considered but is deemed to insert new matter into the claims since the Specification as originally filed does not provide support for the modified glycosaminoglycan as instantly claimed. Claim 1 has been amended to include a limitation wherein "0.1% to 100% of the glycosaminoglycan's hydroxyl groups are substituted with $-L^1C(O)NH\text{-}NH\text{-}C(O)\text{-}L^2Q$". However, the originally filed Specification does not support such a limitation. Applicants indicated that support for the degree of substitution can be found on p. 23, lines 23-32. However, an examination of the cited page clearly states, "one primary hydroxyl group of the glycsoaminglycan to 100% of the primary hydroxyl groups can be substituted with the hydroxide-reactive group" (emphasis added). The cited section further goes on to state "when one or more primary hydroxyl groups of the glycsoaminoglycan are substituted, one or more secondary hydroxyl groups can also be substituted with the hydrazide-reactive group". The Specification is silent with regards to the degree of substitution with respect to secondary hydroxyl groups on the glycosaminoglycan. Furthermore, there is no suggestion of the desired degree of substitution for the secondary hydroxyl groups. Thus, there is no support for the broad

limitation claimed in Applicants' amendment, wherein 0.1% to 100% of all hydroxyl groups of the glycosaminoglycan bear the recited substitutent. Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is point out its nonexistence. *In re Alton*, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-10, 24, 25, 53, 200, 227, 228, 239, 240 and 242-244 are rejected under 35 U.S.C. 103(a) as being unpatentable over PG Pub No. US 2003/0087877 A1 to Calias *et al.* (PTO-892, Ref. A), in view of U.S. Patent No. 5,874,417 to Prestwich *et al.* (hereinafter referred to as the '417 patent; IDS dated 19 March 2009).

Calias *et al.* teach chemical modification of biopolymers for the delivery of therapeutic agents to specific tissues, organs or cells within a subject, or to extend the bioavailability of the therapeutic agent by enhancing its *in vivo* stability (paragraph 0001). The biopolymer is initially modified to introduce one or more disulfide bonds into a side chain of the biopolymer, which facilitates the reaction of the biopolymer with a therapeutic agent that has also been modified to present a reactive thiol moiety to form the biopolymer-therapeutic agent conjugate. The site-specific reaction of the biopolymer and the therapeutic agent increases the stability of the therapeutic agent upon delivery to the desired site targeted by the biopolymer. Drug delivery specificity is

achieved by appropriate selection of the structure and molecular weight of the biopolymer (paragraph 0013). Typical acceptable biopolymers include hyaluronic acid and any of its hyaluronate salts, carboxymethyl cellulose, carboxymethyl amylase, chondroitin sulfate, dermatan sulfate, heparin and heparin sulfate, carboxymethyl chitosan, carrageenan, and sodium alginate, among others (paragraph 0018). The common feature of the biopolymers considered to be useful is that they are biocompatible, they contain carboxylic acid functionality, and they can be modified to react with an organic disulfide compound.

The biopolymers can be "activated" by reacting the biopolymer with a suitable activating agent to render the carboxylic group on the biopolymer vulnerable to nucleophilic attack, such as by using carbodiimides (paragraph 0034). The activated biopolymer is then reacted with an organic disulfide compound having the formula R-L-S-S-M, wherein R is an amino, hydroxyl or carbonyl group, L, if present, is a spacer, each S is a sulfur atom, and M is an organic moiety (paragraph 0035-0037). An example of such a biopolymer-therapeutic agent conjugate is hyaluronic acid (HA) conjugated to 3-nitro-2-pyridinesulfenyl-ethylamine (NEA) (paragraph 0042). Methods for the synthesis of HA-NEA with 1%-2% NEA modification and 15%-20% NEA modification are disclosed in Examples 2 (paragraph 0060) and 3 (paragraph 0061), respectively. The biologically active conjugates can be formulated as pharmaceutical compositions for medical diagnosis or treatment, together with appropriate pharmaceutically acceptable carriers and, optionally, other therapeutic or diagnostic agents (paragraph 0051). The disclosed process can also be employed to modify the

surface of a medical device or instrument (paragraph 0052), such as stents (paragraph 0054).

The teachings of Calias *et al.* differ from that of the instantly claimed invention in that the carboxylic acid group of the biopolymer is conjugated to an amino or hydroxyl group of the organic disulfide compound, instead of being conjugated to a hydrazide group, as instantly claimed.

The Prestwich '417 patent teaches a composition comprising a hyaluronate functionalized with a hydrazide at glucuronic acid sites of said hyaluronate, wherein the hydrazide is chosen from a group consisting of monohydrazide and hydrazides comprising three or more amine groups. The hyaluronate functionalized with dihydrazide may be coupled, through an amine moiety of the dihydrazide, to additional components such as biocompatible materials and biologically active materials, e.g., drugs (column 3, lines 31-34). A method for making a functionalized hyaluronate involves providing hyaluronate in an aqueous solution, mixing the hyaluronate in aqueous solution with a dihydrazide to form a hyaluronate-dihydrazide mixture, adding a carbodiimide to the hyluronate-dihydrazide to react with each other in the presence of the carbodiimide under conditions producing hyaluronate functionalized with dihydrazide (column 3, lines 45-54).

The hyaluronate functionalized with dihydrazide has a pendant hydrazido group which is useful in subsequent reactions. Advantageously, a number of manipulations on the hyaluronic acid (HA) molecule can proceed from the functionalized hyaluronate. In addition, the mild conditions used throughout prevent degradation of HA (column 3,

lines 55-60). Furthermore, the functionalized or crosslinked HA facilitates subsequent attachment of additional components, such as bioeffecting agents, including drugs. The presence of a pendant hydrazido group on the HA molecule offers a number of advantages (column 3, lines 62-66). The lower pK_a of the hydrazido group allows subsequent coupling and crosslinking reactions which can be conducted under neutral conditions that are not detrimental to the molecular weight integrity of the HA molecule. Another advantage is that the pendant hydrazido moiety is reactive in aqueous solution at mildly basic pH toward a number of amino specific probes (column 4, lines 6-16). Still another advantage is that the space between the HA functionalized site and the pendant hydrazido group can be varied as desired depending on what kind of steric assessibility is desired for further reactions (column 4, lines 21-29). The hydrazide functionalized hyaluronate mixture may be crosslinked, and the crosslinking may produce gels (column 5, lines 1-2). Additional components may be added to the mixture before, during or after crosslinking (column 5, lines 3-5). Examples of hydrazide compounds that can be conjugated to HA are shown in Figure 5 (column 5, lines 25-56). The Prestwich '417 patent further notes that the disulfide-containing hydrazides, such as those shown in Figs 5H and 5R, may be utilized to create readily reversible linkages to HA, either linking them to themselves or to other agents that have been attached (column 21, lines 57-61).

The functionalized HA or crosslinked HA may be used as a carrier for a wide variety of releasable biologically active substances having curative or therapeutic value for human or non-human animals (column 13, lines 26-40). Or, for use in tissue

engineering, crosslinked biodegradable derivatives of hyaluronate can be produced with defined pore size which may vary according to the choice of crosslinker and mode of preparation of the crosslinker (column 14, lines 52-65). The defined pores can provide support to cells such as keratinocytes, chrondrocytes and osteoblasts which can adhere and subsequently grow in three dimensions for use in skin grafts, nerve repair and cartilage and bone repair. Thus, the composition comprising a hyaluronate functionalized with a hydrazide can further include a plurality of cells for tissue engineering (claim 5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Calias *et al.*, concerning chemical modification of biopolymers with disulfide groups for the delivery of therapeutic agents to specific tissues, organs or cells within a subject, or to extend the bioavailability of the therapeutic agent by enhancing its *in vivo* stability, with the teachings of the Prestwich '417 patent, regarding a composition comprising a hyaluronate functionalized with a hydrazide at glucuronic acid sites of said hyaluronate. Since the teachings of Calias *et al.* and the Prestwich '417 patent are in the same field of endeavor, teaching the conjugation of biologically active materials to biopolymers, such as HA in the case of the Prestwich '417 patent, and HA, dermatan sulfate, and carboxymethyl chitosan, among others, in the case of Calias *et al.*, via a disulfide linkage for drug delivery, one of ordinary skill in the art would have been motivated to combine the teachings and use one of the disulfide hydrazide compounds disclosed in the Prestwich '417 patent, such as shown in Figs. 5H and 5R, for conjugation onto carboxymethyl chitosan. One of

ordinary skill in the art would have been motivated to substitute the amino disulfide linkers disclosed by Calias *et al.* with the disulfide hydrazide linkers disclosed in the Prestwich '417 patent in order to receive the expected benefit, as suggested in the Prestwich '417 patent, that the use of hydrazides for conjugation with the carboxylic acid group of the biopolymer, such as HA, is advantageous because the mild conditions used throughout the reactions prevent degradation of HA, the lower pK_a of the hydrazido group allows subsequent coupling and crosslinking reactions which can be conducted under neutral conditions that are not detrimental to the molecular weight integrity of the HA molecule, and the pendant hydrazido moiety is reactive in aqueous solution at mildly basic pH toward a number of amino specific probes. Furthermore, as the Prestwich '417 patent demonstrated the conjugation of a hydrazide compound with the carboxylic acid moiety of HA, and carboxymethyl chitosan similarly contains a reactive carboxylic acid moiety, one of ordinary skill in the art would have a reasonable expectation of success in conjugating any of the linkers disclosed in the Prestwich '417 patent, such as that in Figs. 5H and 5R, with carboxymethyl chitosan.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Allowable Subject Matter

Claims 224-226, 229, 230, 234, 235 and 237 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

SCARLETT GOON
Examiner
Art Unit 1623